

# Searching for Scale

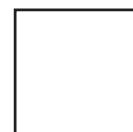
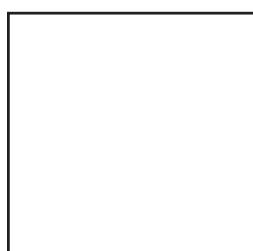
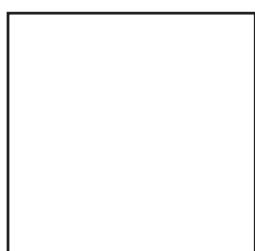
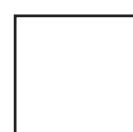
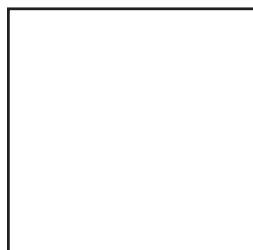
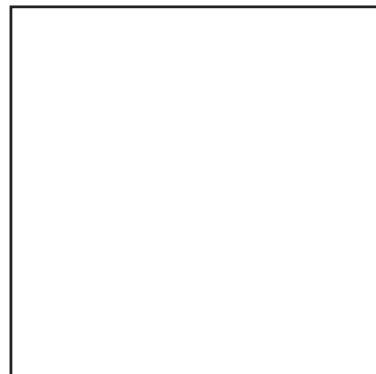
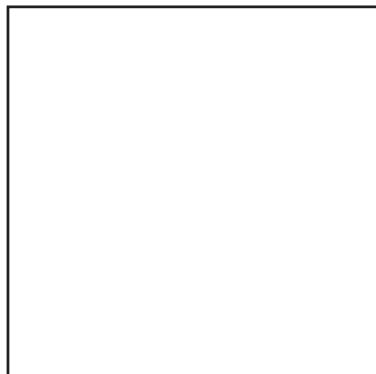
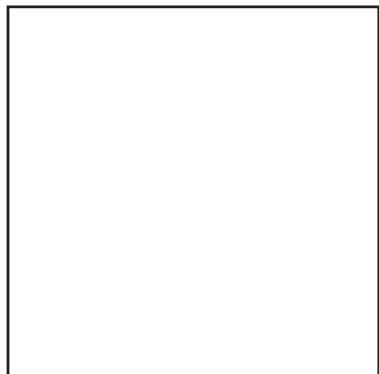
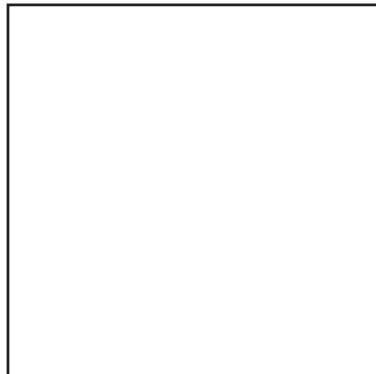
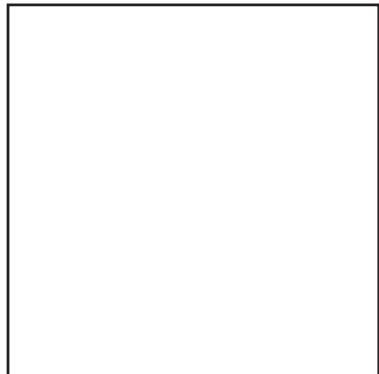
Name: \_\_\_\_\_ Date: \_\_\_\_\_

Biological Structure	Actual Diameter (in Meters)	Size Relative to Cell	Object Used to Model Biological structure	Measured Size of Model Object	Size Relative to Model Cell (the Room)
Cell	$1 \times 10^{-5}$	$\frac{1 \times 10^{-5}}{1 \times 10^{-5}} = 1$	Room	10 meters	$\frac{10}{10} = 1$
Bacterium	$1 \times 10^{-6}$	$\frac{1 \times 10^{-6}}{1 \times 10^{-5}} = \frac{1}{10}$	Desk	1 meter	$\frac{1}{10} = \frac{1}{10}$
Mitochondrion	$5 \times 10^{-7}$	$\frac{5 \times 10^{-7}}{1 \times 10^{-5}} = \frac{1}{20}$			
Virus	$1 \times 10^{-7}$				
Ribosome	$1 \times 10^{-8}$				
Protein	$5 \times 10^{-9}$				
Glucose molecule	$1 \times 10^{-9}$				
H <sub>2</sub> O molecule	$1 \times 10^{-10}$				

# **Probing for Answers Score Sheet**

	<b>A</b>	<b>B</b>	<b>C</b>	<b>D</b>	<b>E</b>	<b>F</b>	<b>G</b>	<b>H</b>	<b>I</b>
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<b>8</b>									
<b>9</b>									

# **Probes**



# **Probing for Answers—Level 1**

	<b>A</b>	<b>B</b>	<b>C</b>	<b>D</b>	<b>E</b>	<b>F</b>	<b>G</b>	<b>H</b>	<b>I</b>
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<b>9</b>									

**Level 1**

## **Probing for Answers—Level 2**

	<b>A</b>	<b>B</b>	<b>C</b>	<b>D</b>	<b>E</b>	<b>F</b>	<b>G</b>	<b>H</b>	<b>I</b>
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**Level 2**

# **Probing for Answers—Level 3**

	<b>A</b>	<b>B</b>	<b>C</b>	<b>D</b>	<b>E</b>	<b>F</b>	<b>G</b>	<b>H</b>	<b>I</b>
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<b>8</b>									
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**Level 3**

## **Probing for Answers—Level 4**

	<b>A</b>	<b>B</b>	<b>C</b>	<b>D</b>	<b>E</b>	<b>F</b>	<b>G</b>	<b>H</b>	<b>I</b>
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<b>8</b>									
<b>9</b>									

**Level 4**

## **Probing for Answers—Level 5**

	<b>A</b>	<b>B</b>	<b>C</b>	<b>D</b>	<b>E</b>	<b>F</b>	<b>G</b>	<b>H</b>	<b>I</b>
<b>1</b>									
<b>2</b>									
<b>3</b>									
<b>4</b>			C			F			
<b>5</b>			C			F			
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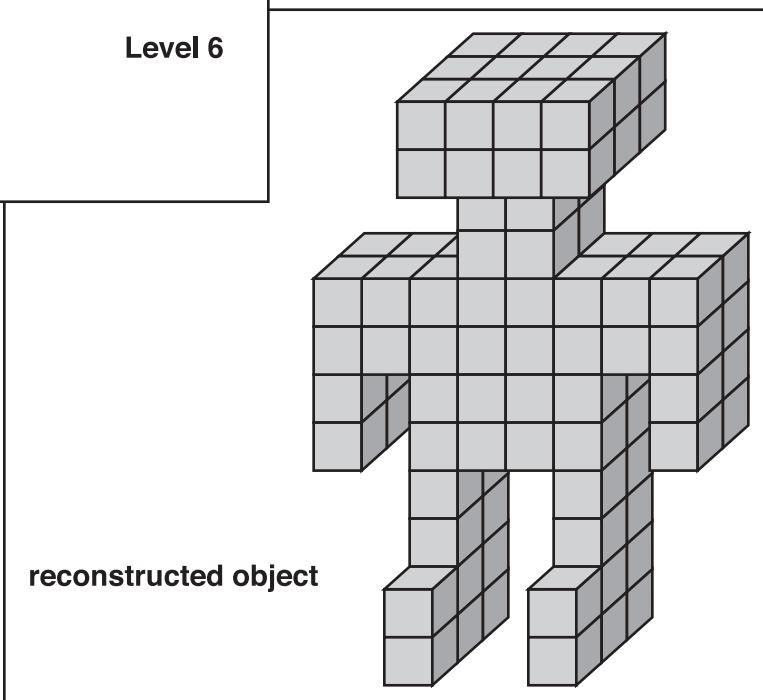
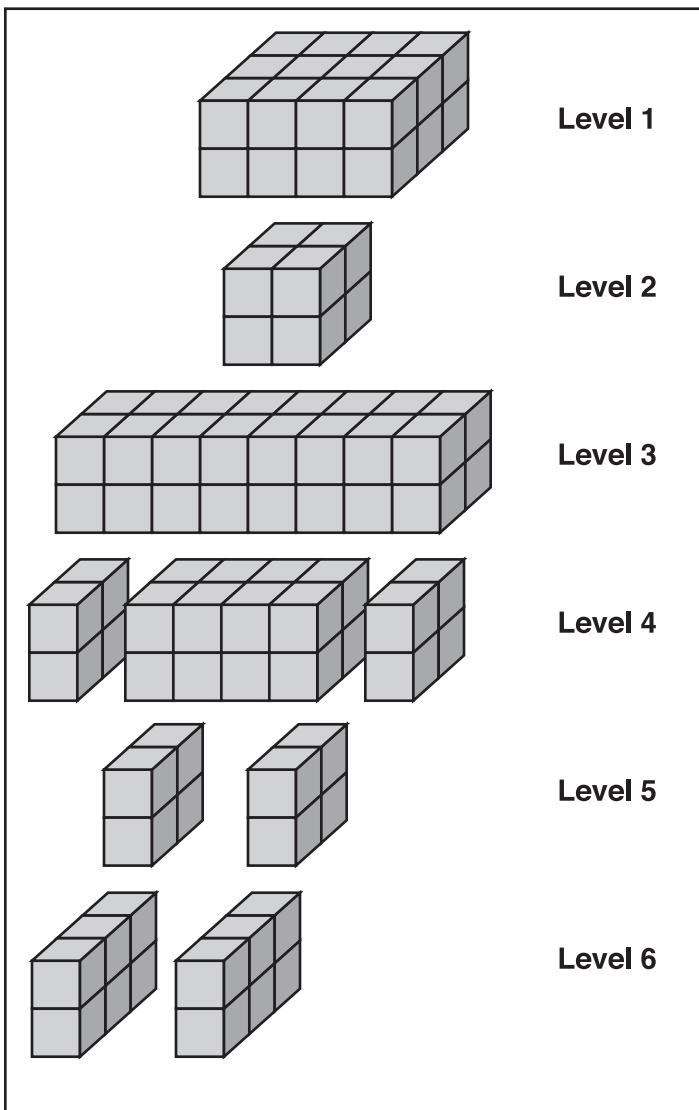
**Level 5**

# **Probing for Answers—Level 6**

	<b>A</b>	<b>B</b>	<b>C</b>	<b>D</b>	<b>E</b>	<b>F</b>	<b>G</b>	<b>H</b>	<b>I</b>
<b>1</b>									
<b>2</b>									
<b>3</b>									
<b>4</b>			C			F			
<b>5</b>			C			F			
<b>6</b>			C			F			
<b>7</b>									
<b>8</b>									
<b>9</b>									

**Level 6**

# Solution to Probing for Answers



reconstructed object

# **Memo from the Director, Global Science and Health Organization**



## **Memo**

**TO:** Members, Scientific and Health Evaluation Teams

**FROM:** Director, Global Science and Health Organization

**RE:** New disease

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Our Division of Disease Surveillance recently reported a new disease affecting approximately 30% of the persons living in a small rural area of the United States. Affected individuals have a lack of energy and demonstrate a progressive loss of muscle function. Although we have no information yet, we believe the disease is caused by an infectious agent. Consequently, to limit the spread of this disease, immediate intervention is critical.

We need your expertise to answer these questions:

1. Is there evidence of disease at the cellular level? If so,
2. Is the disease caused by an infectious agent? If it is,
3. What is the infectious agent?
4. Does the infectious agent attack muscle tissue?
5. How might the infectious agent cause the disease?
6. Is there a drug to treat or prevent the disease?

Blood and muscle tissue samples from unaffected and affected individuals are waiting for you. The microscopy and X-ray crystallography facilities at GSHO are being readied for your arrival. In order to gain information as quickly as possible, please develop a solid research plan before beginning your investigations.

Good luck!

# **Research Plan**

Name: \_\_\_\_\_ Date: \_\_\_\_\_

1. To answer the question, \_\_\_\_\_  
\_\_\_\_\_
2. I will use this technology: \_\_\_\_\_  
\_\_\_\_\_
3. I chose this technology because \_\_\_\_\_  
\_\_\_\_\_
4. My hypothesis is \_\_\_\_\_  
\_\_\_\_\_
5. I expect one of the following two results: \_\_\_\_\_  
\_\_\_\_\_
6. Observations (actual results) and interpretation:

# **Example of a Research Plan**

1. To answer the question, Is there evidence of disease at the cellular level (in muscle cells)?
2. I will use this technology: Light Microscope
3. I chose this technology because its resolution level allows me to see muscle cells.
4. My hypothesis is There is evidence of disease in muscle cells.
5. I expect one of the following two results: I will see abnormal muscle cells in affected individuals OR I will see NO abnormal muscle cells in affected individuals.
6. Observations (actual results) and interpretation:  
**Result 1—**Muscle cells from affected individuals are different from normal muscle cells and those from unaffected individuals; interpreted as evidence of disease in muscle of affected individuals. Proceed to next question.
  1. To answer the question, Is the disease caused by an infectious agent (bacteria)?
  2. I will use this technology: Light Microscope
  3. I chose this technology because its resolution level allows me to see bacteria.
  4. My hypothesis is (continue as above).

## **OR**

6. Observations (actual results) and interpretation:  
**Result 2—**Muscle cells from affected individuals appear the same as normal muscle cells and muscle cells from unaffected individuals. Interpreted as lack of evidence of disease in muscle cells of affected individuals. Look for evidence of disease in other tissues.
  1. To answer the question, Is there evidence of disease at the cellular level (blood)?
  2. I will use this technology: Light Microscope
  3. I chose this technology because its resolution level allows me to see blood cells.
  4. My hypothesis is (continue as above).

# **Drug Discovery Evaluation Form**

Name: \_\_\_\_\_ Date: \_\_\_\_\_

Molecule 1: Evaluation of X-ray crystallography, protein structure data:

Molecule 2: Evaluation of X-ray crystallography, protein structure data:

Molecule 3: Evaluation of X-ray crystallography, protein structure data:

Molecule 4: Evaluation of X-ray crystallography, protein structure data:

Overall evaluation: Is there a drug you would recommend to treat the disease? Justify your response.

# Available Technologies

Probe	Visible Light	Visible Light	Electrons	X-rays	Approximate Resolution
eye	Light Microscopes	Electron Microscopes	X-Ray Techniques		$10^{-10} \text{ m}$
					$10^{-11} \text{ m}$

Master 3.5

# Science Reference Manual

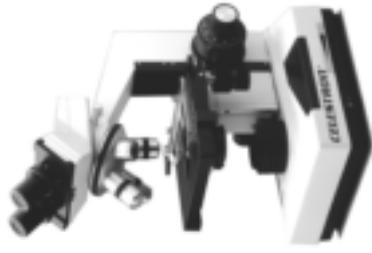
## Science Reference Manual

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  - Muscle Proteins
  - Muscle Contraction
- Section 5: Drug Discovery
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## Light Microscopy



The first microscopes were optical ones, which use glass lenses to focus and magnify light. Although Hans and Sacharias Janssen constructed the first optical microscope in 1595, it was not until 60 to 80 years later that major discoveries were made with this technology. In the late 1600s, Antonio van Leeuwenhook improved the lenses used in microscopes, allowing magnification to be increased from 50 $\times$  to 200 $\times$ . There were additional improvements to optical microscopy over the next 300 years, which ultimately increased magnification up to 1,500 $\times$  and allowed optical microscopes to resolve objects as small as 200 nanometers ( $\text{nm}$ ;  $2 \times 10^{-7} \text{ m}$ ). This resolution is a physical limit dictated by the wavelength of light (that is, its size as a probe).



## Electron Microscopy

The first electron microscope (EM) was built in 1933 by Ernst Ruska (1986 Nobel Prize winner for achievements in electron optics). Ruska used accelerated electrons and magnetic coils to make an image instead of light and glass lenses. Electrons have a wavelength (size) that is  $10^4$  to  $10^5$  times smaller than the wavelength of light. EMs can resolve objects that are  $10^3$  times smaller than the smallest resolvable object in a light microscope.

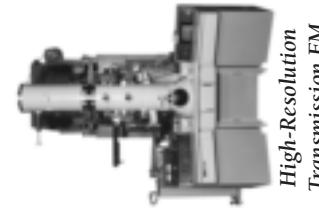
Transmission EMs yield information similar to transmission light microscopes about the size, shape, and arrangement of particles in a specimen, although at much higher resolution. The high-resolution transmission EM can magnify a sample up to 50,000 $\times$  and provide a resolution of 0.1 nm ( $0.1 \times 10^{-9} \text{ m}$ ).



Cryo-EM

The resolution of EMs can be improved through modifications of the sample preparation procedure. In cryo-EM, specimens are frozen rapidly to eliminate ice crystals from forming that can distort the specimen's structure. Samples are then viewed at temperatures as low as  $-185^\circ\text{C}$ .

Two- and three-dimensional models of the sample can be reconstructed using a computer program that averages many electron micrographs taken from different angles.



High-Resolution Transmission EM

## Master 3.6(a)

# Science Reference Manual

Electron microscopy requires a sample thin enough to allow electrons to pass through. Samples smaller than 1/500<sup>th</sup> the diameter of a human hair are used. In a transmission EM, electrons pass through the sample and are imaged on a fluorescent screen at the bottom of the microscope column. Samples that are more electron dense allow fewer electrons to pass through. This results in a darker image. In some cases, chemicals that are electron dense and bind to specific cellular components are used as stains. These stains make it possible to view cell components that themselves are not electron dense.

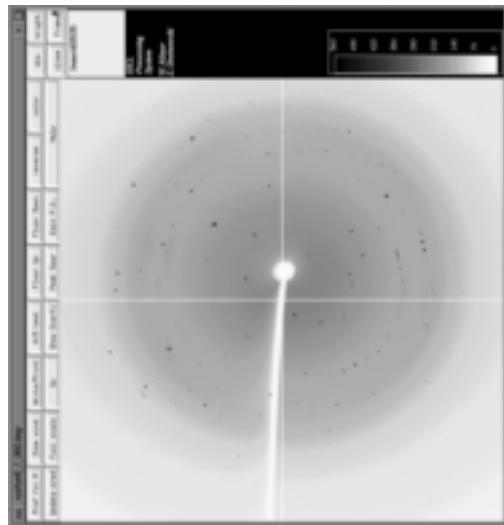
## X-Ray Crystallography



X-rays, with wavelengths approximately the same size as the spacing between atoms, are directed through a crystal of the substance under study. The X-rays are bent by the electrons surrounding the atoms in the crystal. The scattered X-rays produce a pattern as they exit the crystal. Locations at which X-rays are received by a detector are recorded as dark spots on a film. Sophisticated computer programs use measurements of the angles of the scattered X-rays and their intensities to calculate the three-dimensional positions of the atoms in the crystal. By rotating the crystal and making many two-dimensional images, it is possible to combine results to produce a three-dimensional picture of the molecule.

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This is a typical diffraction pattern produced by passing X-rays through a protein crystal. The dark spots represent intensities of X-rays and places where X-rays have struck the detector. Scientists measure the location and intensity of the scattered X-rays. The white circle to the right of center with the white line extending to the left is a shadow from a "beamstop." The beamstop is a small piece of lead mounted on a metal arm. It protects the detector from the intense beam of unscattered X-rays.



Sophisticated computer programs convert the data from X-ray crystallography patterns into three-dimensional models of proteins, such as the one above of MutY, a DNA-repair protein.

## Master 3.6(b)

# Science Reference Manual

## Infectious Disease

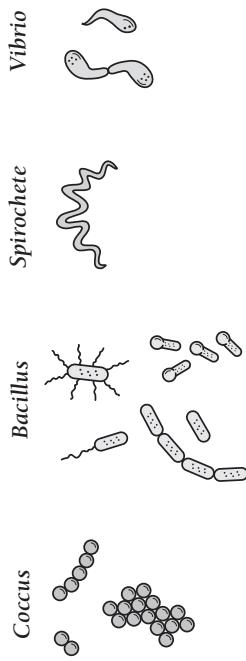
Infectious diseases result when an organism or other agent enters the body and reproduces itself. Infectious agents, or pathogens, can produce disease in several ways. For instance, pathogens can produce chemical agents, such as proteins or other small molecules, which can damage tissue. Also, the chemical agents can interfere with normal cellular processes or act as toxins.

The most common pathogens are bacteria and viruses. Other pathogens include fungi, worms, and protozoans.

## Bacteria

Bacteria are single-celled prokaryotic organisms. Most bacteria are from  $0.3$  to  $2.0 \times 10^{-6}$  m in diameter. Most are harmless, and many perform helpful functions. Only a small number of bacteria are pathogens. Cholera, leprosy, pneumonia, tuberculosis, and whooping cough are examples of human diseases caused by bacteria that destroy healthy cells. Diphtheria, scarlet fever, tetanus, and botulism are human diseases caused by toxins that bacteria produce.

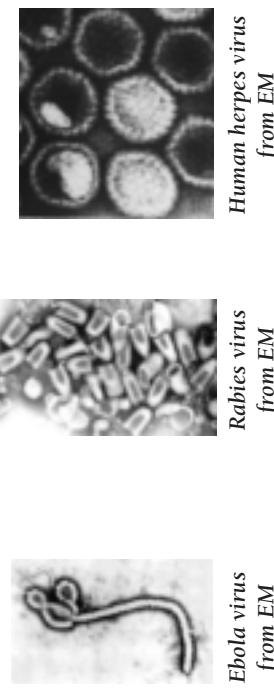
Bacteria are divided into groups according to shape, as seen below. Some bacteria may be found in small groups or clusters.



## Viruses

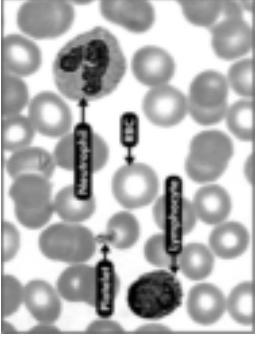
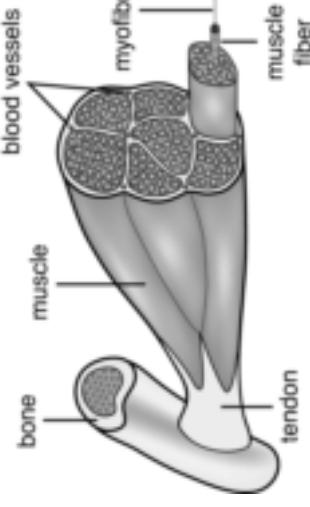
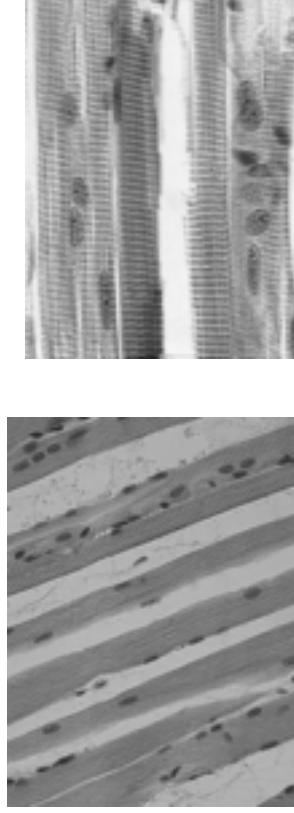
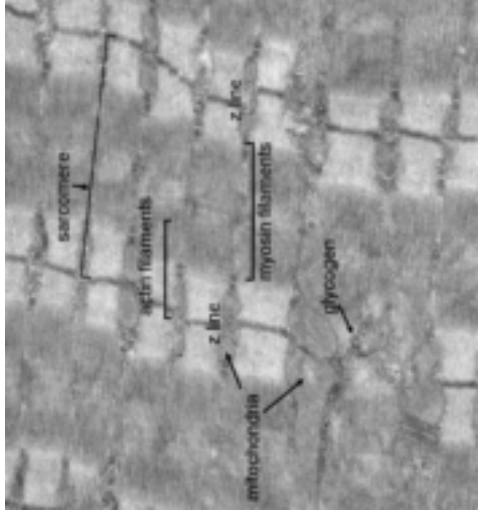
Viruses are small particles consisting of a core of nucleic acid and an outer coat of protein. They live within cells of living organisms. Viruses generally are rods or spheres that range in size from about  $0.1$  to  $3 \times 10^{-7}$  m. The word virus is derived from a Latin word meaning poison. This is appropriate since viruses are a major cause of disease, even though some viruses are harmless. Diseases in humans that viruses cause include AIDS, chickenpox, colds, influenza, cold sores, measles, mumps, and rabies.

The protein coat of a virus gives the particle its characteristic shape, as illustrated in the following examples:



**Master 3.6(c)**

# Science Reference Manual

Blood	Muscle Structure
 <p>Transmission EM of lymphocyte and red blood cell (RBC) (2,000x).</p>  <p>Skeletal muscle, also known as striated muscle, is made of many muscle fibers, each of which extends the length of the muscle (up to 2.5 feet long). Muscle fibers are arranged parallel to one another, and a membrane called the sarcolemma bundles them together. Each fiber contains multiple nuclei and numerous mitochondria, because each muscle fiber develops from the fusion of many cells called myofibrils that extend the length of the fiber.</p>	<p><i>Blood smear viewed at 400x with a light microscope.</i></p> <p>Approximately 55 percent of blood is a straw-colored clear liquid called plasma. The remainder of blood is composed of various cell types, as seen above.</p> <p>Red blood cells are disc-shaped and contain hemoglobin, a protein to which oxygen binds. Neutrophils and lymphocytes are the major white blood cells. These provide the body's major defense against infection. Platelets are small cells involved in blood clotting.</p>
 <p>Light micrograph of a longitudinal section of normal skeletal muscle; dark oval structures are nuclei.</p>  <p>Electron micrograph of human skeletal muscle.</p>	<p>Each myofibril is made of two kinds of parallel filaments. Thick filaments are <math>1.6 \times 10^{-6}</math> m long and made of myosin. Thin filaments are <math>1 \times 10^{-6}</math> m long and made of actin. Thin filaments extend in both directions from a protein that forms a region called the z line.</p> <p>The area between two z lines is a sarcomere. This is the functional unit of skeletal muscle. Sarcomeres are the smallest units that can perform all of the functions of muscle tissue.</p>

**Master 3.6(d)**

# Science Reference Manual

## Muscle Proteins

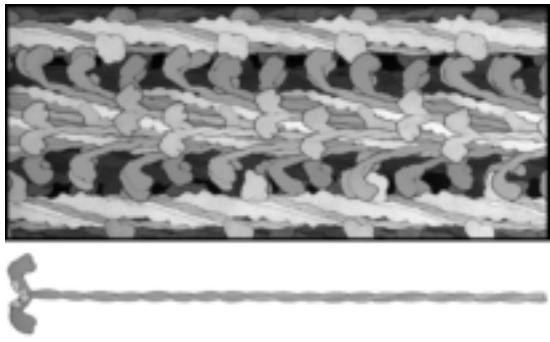
Muscle fibers are made up of many different proteins arranged in a specific way. Their arrangement and individual properties allow muscle to function. Some proteins serve structural roles, while others are directly involved in muscle contraction and relaxation.

Up to one-fifth of the protein in muscle cells is actin, which forms the thin filaments of the cells.

About 360 actin molecules combine to form a long chain. Two of these chains are twisted into a double helix to form an actin filament. Specialized proteins stabilize the filament.



Cryo-EM reconstruction of an actin double helix.



Cryo-EM reconstruction of a myosin molecule (left) and a thick myosin filament in between two thin actin filaments (right).

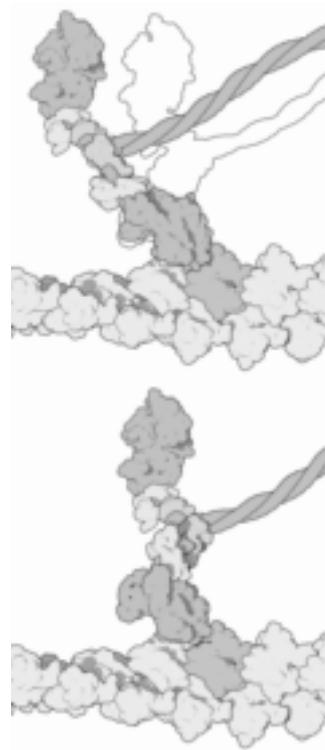
Myosin makes up about 45 to 50 percent of muscle contractile proteins and is the major protein of the thick filaments.

Myosin uses chemical energy to perform motion. The myosin molecule looks somewhat like two golf clubs with their shafts wrapped around each other.

Several other proteins help maintain the structure of the thick filaments.

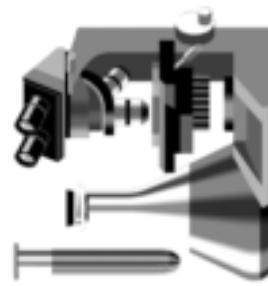
## Muscle Contraction

At the tip of the myosin molecule is a cleft that binds to the actin filament. The lever arm of the myosin pushes the myosin molecule along the actin filament. Muscle contraction requires actin, myosin, and other proteins, the important mineral calcium, and energy in the form of adenosine triphosphate (ATP).



## Rational Basis for New Drug Development

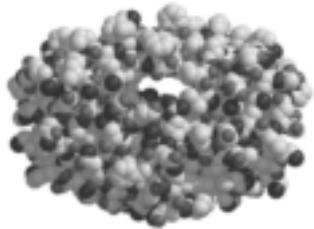
The key to rational drug design is understanding the structure and function of biological molecules involved in disease development. To develop drugs that fight disease, scientists search for chemical and biological substances that target cellular and molecular factors that play a role in disease. Many tools are used in rational drug design, including microscopic techniques, X-ray techniques, computer analyses, and simulations.



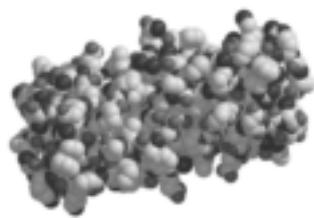
The aim of rational drug design is to produce drugs with greater selectivity and, therefore, greater effectiveness. The approach differs from the traditional medicinal approach, which relies on more extensive and random testing.

# Muscle Protein Structures Determined by X-Ray Crystallography

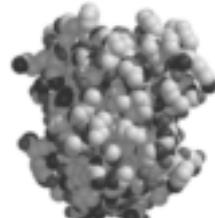
Muscle protein from affected people



Along z-axis

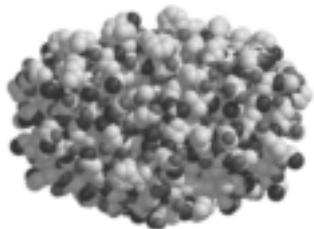


Along x-axis

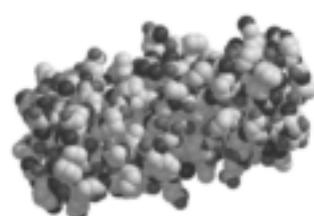


Along y-axis

Muscle protein from unaffected people



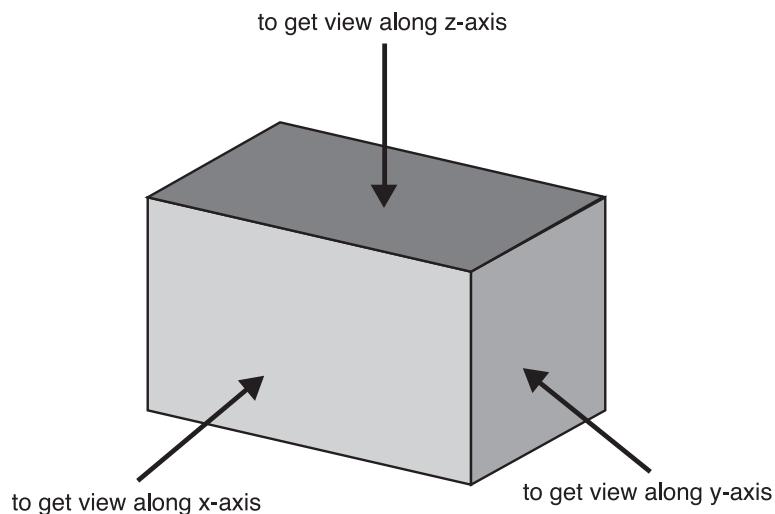
Along z-axis



Along x-axis



Along y-axis



# Microscopes Across Time



1754  
Culpepper microscope



1850  
Ross microscope



1909  
Leitz Wetzler microscope



1948  
Spencer microscope



2004  
Modern research microscope

# **Some Key Developments in Biology, Medicine, and Technology, by Year**

## **BIOLOGY**

- 1665 Cells first described (Robert Hooke).
- 1839 Proposal made that animal tissues are composed of cells (Theodor Schwann).
- 1869 DNA discovered (Friedrich Miescher).
- 1911 Structure of the atom discovered (Ernest Rutherford).
- 1942 Myosin *and* actin reported to be the main structural proteins of muscle (Albert Szent-Gyorgyi and colleagues).
- 1953 Double helix model of DNA proposed (James Watson and Francis Crick; their model was supported by X-ray crystallography done by Maurice Wilkins and Rosalind Franklin).
- 1953 Structure of hemoglobin determined using X-ray crystallography (Max Perutz and John Kendrew).
- 2000 Atomic structure of the large subunit of a bacterial ribosome resolved using X-ray crystallography (Thomas Steitz and colleagues).

## **MEDICINE**

- 1862 Germ theory published: infection is caused by bacteria (Louis Pasteur).
- 1868 First diagnosis made of a complex disease, multiple sclerosis (Jean Martin Charcot).
- 1892 Viruses discovered (Dimitri Ivanovsky).
- 1892 White blood cells identified (Elie Metchnikoff).
- 1893 First modern American medical school opens (Johns Hopkins University, Baltimore, Md.).
- 1895 First pharmaceutical research laboratory founded (Parke-Davis Company, Detroit, Mich.).
- 1928 Penicillin discovered (Alexander Fleming).
- 1959 First major drug to treat leukemia invented (Gertrude Elion).

## **TECHNOLOGY**

- 1593 Thermometer invented (Galileo).
- 1883 First induction motor constructed, the basis of generating electricity (Nicola Tesla).
- 1895 X-rays discovered (Wilhelm Conrad Roentgen).
- 1912 X-ray crystallography invented (William Bragg).
- 1923 First electric refrigerator produced (Electrolux, Old Greenwich, Conn.).
- 1927 First working model of television (Philo Farnsworth).
- 1932 Electron microscope invented (Max Knoll and Ernst Ruska).
- 1969 First microprocessor designed, the basis for computer development (Marcian Hoff).